

APPENDIX G

Chronology of significant regulatory activities between Applicant and FDA during the IND and NDA periods:

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- 09/30/98 Submitted original IND for ERL080A, the sodium salt of mycophenolic acid (MPA) for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal transplants.
- 09/30/98 Also included the following preclinical reports: Pharmacology -"In vitro and in vivo efficacy of ERL 080, Mycophenolate Mofetil and mycophenolic acid", Release Ready Report, 23/1/98. ***"Efficacy of ERL 080 and Mycophenolate Mofetil, with or without cyclosporine (Neoral), SDZ RAD and/or brequinar sodium in rat transplantation models", Release Ready Report, 14.8.98.
- 09/30/98 Also included documentation for drug product comparator - Mycophenolate Mofetil, 250 mg capsules, KN 3746351.00.004, KN 3746351.00.005, KN 3746351.00.006, 21-Aug-98.
- 09/30/98 Also included "Effect of ERL 080 and Mycophenolate Mofetil in rat aorta transplantation", Release Ready Report, 10/3/98. ***"Exploratory side effect study on ERL 080 and Mycophenolate Mofetil with or without cyclosporine (Neoral) in the rat", Release Ready Report, 22/11/97.
- 09/30/98 Also included Study 1463/51-D5140, "ERL 080: Induction of chromosome aberrations in cultured human peripheral blood lymphocytes", extension of study 1463/39. **Study 1463/52-D5140, "CellCept: Induction of chromosome aberrations in cultured human peripheral blood lymphocytes", extension of study 1463/40. **Study MK 50 and MK 54, "ERL 080 Mouse bone marrow micronucleus test by the oral route. **Study MK 55, "CellCept: Mouse bone marrow micronucleus test by the oral route". VOL 18.
- 09/30/98 Also included Study Protocol ERLB 302 entitled, "Multicenter, double-blind, randomized, parallel group study on tolerability and safety of ERLD80A vs. mycophenolate mofetil (CellCept) in maintenance renal transplant patients". Also, Post-text supplement, Protocol ERLB 302, "Multicenter, open-label, follow-up study on the safety of ERLO80A in maintenance renal transplant patients".

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- 09/30/98 Also included CIT Study 16127, "CellCept: 13-Week oral dose-range finding study in rats", 21 August 1998. **Study 974064, "ERL 080: an oral embryo-fetal development study in rats". 23 July 1998. **Study 974063, "CellCept: An oral embryo-fetal development study in rats", 7 August, 1998. **Study 971617, "ERL 080: Mutagenicity test using Salmonella typhimurium" 4/12/97. **Study 971618, "CellCept: Mutagenicity test using Salmonella typhimurium", 4/12/97.
- 09/30/98 Also included Study 981861, "ERL 080: Determination of test compound blood levels in mice for assessing exposure in the bone marrow micronucleus test". **Study 1463/046 and 1463/047, "Expert commentary on the genotoxicity of CellCept and ERL 080".
- 09/30/98 Also provided documentation in support of the following formulations: Drug product composition, sites of manufacture, packaging and control, manufacturing formula and method of preparation - ERL 080A, 360 mg film-coated tablets and drug product excipient control, KN 3752615.00.002, placebo, KN 3753977.00.001, dated 21-Aug-98.
- 09/30/98 Also included Stability Report -ERL 080 360 mg film-coated tablets, 3U98 1849, dated 17-Aug-98.
- 09/30/98 Also included Study Protocol 301 entitled, "Multicenter, double-blind, randomized, parallel group study on efficacy and safety of ERL080A vs. mycophenolate mofetil (CellCept) in de novo renal transplant recipients". Also, post-text supplement 1, Protocol ERLB 301, "Multicenter, open-label, follow-up study on the safety of ERLA in de novo renal transplant recipients".
- 09/30/98 Also included Study MIC 116, "ERL 080: Micronucleus test in vitro with V79 Chinese hamster cells". "Study MIC 118, "CellCept: Micronucleus test in vitro with V79 Chinese hamster cells". "Study 1463/43-1052, "ERL 080: Mutation at the thymidine kinase locus of mouse lymphoma L5178Y cells using the Microtitre Fluctuation Technique". **Study 1463/44-1052, "CellCept (SDZ 207-97): Mutation at the thymidine kinase locus of mouse lymphoma L5178Y cells using the Microtitre Fluctuation Technique".
- 09/30/98 Also included the following Toxicology reports: CIT Study (Centre International (de Toxicologie) 16126, "ERL 080: 13-Week oral dose-range finding study in mice", 21 August 1998. **CIT Study 16128, "CellCept: 13-Week oral dose-range finding study in mice", 21 August 1998. **CIT Study 16125, "ERL 080: 13-Week oral dose-range finding study in rats", 21 August 1998.

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- 09/30/98 Also provided Study Protocol 154 entitled, "A two-period, open-label, randomized, crossover study to evaluate the effect of food on the bioavailability of enteric coated ERL 080 tablets in stable renal transplant patients". Also provided for Dr. Radhakrishnan, principal investigator for Protocol 154.
- 09/30/98 Also included DMPK(CH) 1998/012, "ERL 080: 13-Week oral dose-range finding study in rats, addendum to CIT study 16125 TCR", 6/15/98. **DMPK (CH) 1997/397: "ERL 080: An oral embryo-fetal development study in rats, addendum to Study 974064", 5/11/98. **DMPK(CH) 98-865: "Determination of test compound blood levels in mice for assessing exposure in the bone marrow micronucleus test - contribution of BAPK to the toxicology report", 26-Mar-98. VOL 18.
- 09/30/98 Also included the following Pharmacokinetic and Biology Disposition Reports: DMPK(CH) 1997/069, "Validation of an HPLC analytical method for the determination of ERL 080 in biological matrices", 5-Aug-97. **DMPK(CH) N98-019; Oral bioavailability of three different tablet formulations in dogs vs capsule reference", 19-May-98. **DMPK(CH) 1998/010: "ERL 080: 13-Week oral dose-range finding study in mice, addendum to study 1612 TCS", 6/16/98. VOL 18
- 09/30/98 Also included Study 981851, "ERL 080: "Mutation assay at the thymidine kinase locus of L5178Y mouse lymphoma cells, follow-up study". **Study 1463/39-1052, "ERL 080: Induction of chromosome aberrations in cultured human peripheral blood lymphocytes". **Study 1463/40, "CellCept: Induction of chromosome aberrations in cultured human peripheral blood lymphocytes". VOL 17
- 10/16/98 TELECON TO FDA regarding feedback on the acceptability of protocols 301 and 302.
- 10/22/98 TELECON FROM FDA indicating that the agency will discuss the acceptability of phase 3 clinical studies 301 and 302 at their 10/23/98 meeting. The decision will be conveyed to Novartis after the meeting.
- 10/23/98 TELECON FROM FDA informing that Novartis can proceed with phase 3 clinical studies 301 and 302. Also requested is information to address issues as outlined.
- 10/28/98 FDA FAXED LETTER (98-173) which includes several comments relating to the initial submission.
- 10/30/98 FDA LETTER (98-174) acknowledging receipt of the original IND dated 9/30/98. Assigned IND no. 57,005.
- 11/24/98 Copy of Novartis' minutes of the 11/9/98 end-of-phase 2 meeting between FDA and Novartis submitted to FDA.

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- 12/18/98 FDA FAX which includes the medical officer's review comments concerning the proposed phase 3 protocols 301 and 302.
- 01/19/99 Amendment 1 to Protocol ERLB 301 submitted to FDA.
- 01/22/99 Response to the comments included in the 10/28/98 facsimile relating to the IND.
- 01/28/99 Submitted the following new investigators to Protocol ERLB 301: Drs. Bennett, Kumar, Douzdjian.
- 02/05/99 Response to FDA faxed correspondence which included agency recommendations concerning Protocols B301 and B302.
- 02/11/99 FDA FAX which includes statistical comments regarding Protocols 301 and 302.
- 02/19/99 In fulfillment to agreements made at the End-of-Phase II meeting, provided proposed protocol for carcinogenicity study in mice and response to clinical pharmacology issues raised at the End-of-Phase II meeting with the FDA.
- 02/23/99 Submitted the following formulation information to support clinical trials: ERL080 360 mg film-coated tablets, KN 3752615.00.001, Composition and container, comp_cp_967 _1, Drug Product Manufacture, man_cp_967 _1, dated 6-Apr-98.
- 02/23/99 Also included Amendment 1 to Protocol CERL080 0101 and Form FDA 1572 for Dr. Kaplan.
- 02/23/99 New Protocol CERL080 0101, "A two-period, open-label, randomized, crossover study to evaluate the effect of magnesium/aluminum containing antacid on the bioavailability of enteric coated ERL080 tablets in fasting transplant patients" was submitted.
- 03/15/99 Submitted the following new investigators to Protocol ERLB 302: John J. Curtis, MD, Lawrence Kahana, MD, Mark Pescovitz, MD.
- 03/19/99 TELECON WITH FDA regarding FDA minutes from the EOP2 meeting, the protocol for the rat carcinogenicity study and the protocol for the transgenic mouse study.
- 03/22/99 Also provided for Kenneth L. Brayman, M.D., Ph.D., new investigator for Protocol 8301.
- 03/22/99 Protocol 8302, Amendment 1 submitted.
- 03/23/99 Submitted additional alternate drug product formulation information and revised CMC information for the following formulations: drug product KN 3752615.00.003; drug product placebo KN 3753977.00.001; comparator KN 3746351.00.006; comparator placebo KN 3704798.00.002/024.

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- 03/26/99 FDA FAX providing minutes of the 3/23/99 FDA meeting which reflects Executive CAC recommendations and conclusions.
- 03/29/99 Response to FDA Fax of February 11, 1999 which provided comments from the FDA biostatisticians on Novartis' phase 3 clinical trials 301 and 302.
- 03/29/99 FDA FAX which provides FDA's minutes from the November 9, 1998 end-of-phase 2 meeting.
- 04/01/99 FDA FAX which contains comments from the FDA biopharmaceutist on Protocol CERL080 0101.
- 04/15/99 Provided for the following new investigators for Protocol B302: Harold C. Yang, MD, PhD, Robert Mendez, MD, Stuart M. Flechner, MD.
- 04/27/99 Response to FDA fax dated 4/1/99 which provided comments from the biopharmaceutics reviewer on Protocol 0101.
- 05/07/99 FDA FAX which contains comments from the reviewing statistician concerning Studies 301 and 302.
- 05/10/99 Provided comments to the agency's minutes of the 11/9/98 meeting received on March 29, 1999. Copy of the FDA letter is included with the correspondence.
- 05/17/99 Submitted the following new investigator to Protocol 301; Stephen J. Tomlanovich, MD.
- 05/17/99 Also submitted the following investigators to Protocol 302: Laurence K. Chan, MD, PhD, John F. Neylan, MD, Ronald P. Pelletier, MD.
- 05/27/99 Submitted Draft Protocol, Study ERL 0107, "Double-blind, randomized, parallel group study on gastrointestinal tolerability of ERL080 vs mycophenolate mofetil (CellCept) in renal transplant patients".
- 05/28/99 Faxed minutes of the 5/18/99 FDA Executive Carcinogenesis Assessment Committee meeting and its recommendations regarding the 2-year carcinogenicity rat study.
- 06/02/99 FAX from the FDA reviewing chemist requesting clarification of points 20 and 23 of the end of phase II meeting minutes.
- 06/07/99 Submitted the following new investigators to Protocol 302; Dr. Francis H. Wright, Steven Steinberg, MD, John B. Copley, MD.
- 06/17/99 Response to FDA comments included in the May 7, 1999 correspondence (included) regarding Phase III protocols B301 and B302.

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- 07/02/99 FDA LETTER providing comments from the Division's reviewing statistician and clinical pharmacologist on draft Protocol 0107 submitted 5/27/99.
- 07/09/99 Submitted new investigators for Protocol B302: Jon W. Jones, MD and Rosemary Ouseph, MD (co-principal investigators); Matthew R. Weir, MD.
- 07/09/99 TELECON FROM FDA confirming that unless the firm is planning to use doses higher than those proposed in protocols 301 and 302, additional dose proportionality studies are not required.
- 08/10/99 Response to questions on chemical/pharmaceutical and biological documentation raised in the March 29, 1999 FDA minutes of Novartis' November 9, 1998 end of phase II meeting. Also attached is report, Mycophenolate mofetil capsules 250 mg comparison of dissolution profile (comparator product vs original product) dated 24-Jun-99.
- 08/10/99 Submitted revised CMC documents pertaining to the drug substance PN 3105806, drug product formulation KN 3752615.00.003 and comparator formulation KN 3746351.00.006. Also included is drug product stability report for development batches, 5U99 1849, dated 9-Jun-99.
- 08/23/99 Requested a meeting with the FDA to discuss a proposed multiple dose pharmacokinetic study and to obtain FDA assessment of the potential labeling usage. The study is entitled "An open label study evaluating the multiple dose pharmacokinetics of ERL080 (mycophenolic acid sodium) at steady state during sequentially co-administered tacrolimus and Neoral in stable renal transplant patients". A synopsis of the study is included in the submission.
- 08/30/99 Submitted new investigators for Protocol B302: Gabriel M. Danovitch, MD; Alan H. Wilkinson, MD; John F. Dunn, MD.
- 09/10/99 Requested orphan drug designation for ERL080 for use in the prophylaxis of solid organ transplant rejection. In the US investigations have been conducted for this product under IND 57,005 which resides in the Division of Special Pathogen and Immunologic Drug Products. Included are copies of literature references and study protocols for the Phase III protocols.
- 09/21/99 FDA LETTER acknowledging the 9/10/99 application for orphan designation for Mycophenolic acid for the indication of prophylaxis of solid organ transplant rejection. Assigned reference number 99-1292.
- 09/24/99 Provided the following CMC documentation in support of the planned original NDA for ERL080: Registration stability protocol, ERL080, 180 and 360 mg film-coated tablets, RSP1849A, final approval dated 23-Sep-99.

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- 09/28/99 Submitted new Protocol, Study CERL080 0107, "Double-blind, randomized, parallel group study on gastro-intestinal tolerability of ERL080 vs. mycophenolate mofetil (CellCept) in renal transplant patients". Also included is Post-text supplement no. 1; extension protocol 1 to Protocol 0107.
- 10/15/99 Submitted for FDA review and comment, proposed amendment 2 to Protocol ERLB 302, "Multicenter, double-blind, randomized, parallel group study on tolerability and safety of ERLO80A vs mycophenolate mofetil in maintenance renal transplant patients".
- 11/02/99 Submitted the following new investigator to Protocol 301 Hans W. Solinger, MD. Also provided the following new investigators to Protocol 302; Shamkant Mulgaonkar, MD; Sadanand Pelekar, MD.
- 11/15/99 Requested the Office of Orphan Products to refer to the generic name of ERL080, as sodium mycophenolate rather than the sodium salt of mycophenolic acid.
- 11/15/99 Informed the agency that effective November 15, 1999, Maria Figliomeni, Ph D., Associate Director, DRA, will be the individual responsible for ERL080 and will act as the FDA liaison. Dr. Figliomeni supersedes Mr. Henry Weidmuller in this responsibility.
- 11/16/99 FDA LETTER acknowledging Novartis' 11/15/99 communication for Reference # 99-1292 for ERL080 requesting the Office of Orphan Products to refer to the generic name of ERL080 as sodium mycophenolate rather than the sodium salt of mycophenolic acid. The agency has complied with Novartis' request and the acknowledgement letter of the application for orphan designation has been revised to reflect the change.
- 11/23/99 Submitted new investigator for Protocol ERLB 302: Stuart M. Greenstein, MD.
- 11/23/99 Submitted Bennett, William, MD; pancreatitis.
- 11/29/99 Minutes of the 11/29/99 TELECON with FDA to obtain feedback from the agency on the proposal to include information on the use of the ERL/Tacrolimus combination in the ERL label; also to obtain FDA guidance on Novartis' proposal to conduct a study entitled, "An open label study evaluating the multiple dose pharmacokinetics of ERL080 at steady state during sequentially co-administered Tacrolimus and Neoral in stable renal transplant patients".
- 12/06/99 FDA LETTER regarding Novartis' 9/10/99 orphan drug application for sodium mycophenolate in the treatment of prophylaxis of solid organ transplant rejection. FDA is holding the application in abeyance pending receipt of additional information as outlined.

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- 12/13/99 Submitted [Norway] Dr. Blorn Lien; pancreatitis.
- 12/14/99 Amendment which provides changes/updates for the drug substance and drug product. Included are the following updated documentation: ERL 080, 180 and 360 mg gastro-resistant tablets, KN 3752615.00.004 and KN 3751880,00,001, drug product composition, manufacturing formula and method of preparation, 30-Nov-99 and drug product stability data/report, 30-Nov-99. Also included updated documents for drug product placebo and general placebo capsules dated 30-Nov-99.
- 12/15/99 Provided literature references which were submitted to the agency by facsimile prior to the meeting requested by Novartis (ser # 023) in order to facilitate the discussion at the meeting.
- 12/20/99 Informed the agency that it has been decided to terminate the food effect study ERL W154, included in the original IND, prior to its completion. Provided is background information regarding this decision.
- 01/18/00 FDA FAX from the reviewing medical officer indicating that Novartis may proceed with study 302, serial No. 027. However, the agency was unclear as to how the data from the study will be utilized in order to support the firm's future application, as the lower doses proposed are based upon clinical practice and not the approved doses.
- 01/24/00 Submitted [Norway]; Dr. B. Lien; pancreatitis ,follow-up # 1.
- 02/08/00 Submitted Bennett, William, MD; pancreatitis, Follow-up # 1.
- 02/11/00 Submitted new investigators for Protocol 0107: Drs. P.R. Rajagopalan, Douglas Slakey, Timothy Pruett Also provided for Angelo DeMattos, MD, who has replaced William Bennett as principal investigator for Protocol B301.
- 02/15/00 In reference to FDA letter dated December 6, 1999 which indicated that the Office of Orphan Drug Products believes that ERL is not eligible for orphan drug designation unless information is submitted to support the designation, Novartis requested that FDA keep the orphan application open until the ERL development program has progressed further. (Ref. No. 99-1292)
- 02/22/00 Request for a teleconference with the Division to discuss Novartis' proposed amendment 2 to Protocol 8302, Serial No. 027, and the agency FAX dated January 18, 2000.

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- 02/24/00 TELECON FROM the FDA Office of Orphan Drug Products to inform Novartis that the agency will keep the ERL orphan application open. The agency recommended that the firm make contact with the Office of Orphan Drug every 6 months and for future submissions of amendments to the application, reference be made to the firm's previous application using the reference number.
- 03/03/00 Submitted Amendment No. 2 to Protocol B302.
- 03/03/00 Response to FDA faxed correspondence dated July 2, and November 8, 1999 providing comments on draft Protocol and final Protocol 0107 (serial nos 017 and 026). FDA's comments are reinstated followed by Novartis' response.
- 03/07/00 TELECON FROM FDA regarding Novartis' request for a teleconference to discuss agency comments relating to the review of Protocol B302, Amendment 2. The agency indicated that the issues were statistical and that there was a Guidance document on this issue which will be provided to Novartis for internal discussion by the firm in advance of the meeting scheduled for March 24.
- 03/09/00 Submitted Amendment 1 to Protocol 0107.
- 03/09/00 Memo of the November 29, 1999 TELECON MINUTES with the FDA to discuss Study CERL 0108 submitted on August 23, 1999 (Serial No. 023) for which Novartis is seeking FDA consensus on the feasibility of performing the study. Novartis is planning to submit the new protocol for review during the month of January 2000.
- 03/17/00 FDA LETTER providing comments from the reviewing medical officer with regard to Phase III studies 301 and 302 and specifically regarding the number of patients that are necessary to assess the safety of ERL
- 03/22/00 FDA LETTER acknowledging receipt of Novartis' February 22, 2000 correspondence requesting a teleconference. The agency categorized the meeting to be type C based on the statement of purpose, objectives and agenda and scheduled it for March 24, 2000.
- 03/23/00 Submitted new investigators, Protocol 0107: John A. Daller, MD, PhD; John P. Leone, MD, PhD.
- 04/03/00 Submitted new Protocol entitled, "A two phase, open-label, randomized, crossover study to evaluate the effect of food on the bioavailability of enteric coated ERL080 tablets in stable renal transplant patients".
- 04/19/00 Provided the final version of the March 24, 2000 teleconference minutes between Novartis representatives and the Division to discuss the FDA fax received March 17, 2000, and to reach agreement on the number of patients to be included in Novartis' safety database and patients expected to have 12 months exposure to ERL080.

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- 04/26/00 As requested during a teleconference with the FDA, provided the agency with a "working version" of Protocol ERLB 302 incorporating all amendments submitted to date.
- 04/27/00 FDA FAX in reference to Novartis' submission of March 3, 2000, Serial No. 041 (Protocol 0107). The reviewing clinical pharmacologist requested dissolution profiles using approved methods and media of the re-encapsulated CellCept and the commercial CellCept that will be used in the final study report.
- 05/02/00 In response to the clinical pharmacologist's April 27, 2000 request received via facsimile, Novartis indicated that the requested dissolution profiles using the approved methods and media of the re-encapsulated CellCept and commercial CellCept that will be used in the final study protocol have been provided in the submission dated March 23, 1999, Serial No. 010.
- 05/02/00 Submitted new investigator, Protocol 0107: Anthony P. Monaco, MD.
- 06/22/00 Submitted [Norway] Dr. Blorn Lien. Pancreatitis. Follow-up # 2.
- 06/28/00 Submitted new investigators for Protocol 0107: Drs. Duane Wombolt, John J. Curtis.
- 08/11/00 Submitted new investigator for Protocol ERLB 302: Bertram L. Kasiske, MD.
- 08/15/00 Requested a teleconference with the Division to discuss and obtain feedback on Novartis' clinical program (trials B301, B302, 0107) and labeling claims (superior gastrointestinal tolerability) that Novartis expects may emerge from the data generated from study 0107.
- 09/01/00 Annual Report covering the period from October 7, 1998 through October 6, 1999. Included clinical and preclinical information and revised Investigator's Brochure, dated 12-Jul-99.
- 09/13/00 In follow-up to an agreement made by Novartis to keep FDA updated at 6 month intervals on the need to keep the orphan application for ERL080 open, this correspondence requests that the application be kept open until the ERL development program has progressed further (Reference # 99-1291).
- 09/18/00 Minutes of the September 18, 2000 teleconference with the FDA to obtain feedback on the following proposals: reduction in B302 enrollment from 300 patients to 280; a partial initial NDA submission with the remaining 12 month data with the 120 day update; labeling claims for superior GI tolerability when compared to MMF (mycophenolate mofetil).
- 09/22/00 Submitted new investigator for Protocol B302: Reginald Gohh, MD.

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- 10/10/00 Submitted Amendment No. 2 to Protocol 0107.
- 10/25/00 Submitted new investigator to Protocol 0107: John B. Copley, MD.
- 11/01/00 Request for a teleconference with the Division to discuss Novartis' proposal for a GI analysis plan that, if successful, will achieve a GI superiority claim for ERL080 compared to MMF. An agenda for the meeting, a list of objectives and a list of Novartis participants is provided. Novartis proposes November 22nd and 28th as possible dates for the meeting.
- 11/08/00 Submitted Amendment No.3 to Protocol 0107.
- 01/12/01 Submitted new investigator to participate in Protocol 0107: Alan H. Wilkinson, MD.
- 01/23/01 Submitted new Protocol 0106, Part A, "An open-label, two parallel age cohort, single oral dose study to assess the pharmacokinetics of enteric-coated ERL080 180 mg tablets in stable pediatric renal transplant recipients". Part 8, Standard administrative and GCP related instructions for clinical pharmacology studies". Robert B. Ettenger, MD, new investigator.
- 02/23/01 Submitted new investigator to Protocol B302: Antonio Guasch, MD. New investigator to Protocol 0107: Laurence Chan, MD. Also provided changes to Protocol 8302 for Dr. Mysore Kumar.
- 02/27/01 Correspondence requesting that the orphan drug application for ERL (Reference No. 99-1292) be kept open until the product's development program has progressed further. Reference is made to the February 14, 2000 teleconference regarding this request and the agency's response that the request would be honored. Novartis agreed to keep the agency updated on the need to keep the application open at 6 month intervals.
- 04/30/01 Submitted new investigator to Protocol 0107: Thomas H. Waid, MD.
- 05/14/01 Submitted Annual Report covering the period from October 7, 1999 through October 6, 2000. Included clinical and pre-clinical information.
- 05/16/01 Submitted Protocol 0109, Amendment No.1.
- 05/24/01 Submitted new investigator to Protocol 0106: Sharon Bartosh, MD.
- 06/08/01 Submitted Dr. William Bennett. Pancreatitis acute. Follow-up # 1.
- 06/28/01 Submitted William Bennett, MD. Pancreatitis acute. Follow-up # 2.

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- 07/26/01 Submitted correspondence requesting FDA to waive the requirement for submission of evidence demonstrating the bioavailability or bioequivalence necessary to support the registration of the 180 mg dose in addition to the 360 mg dose. Technical data, in vitro data and clinical data are provided to support this request.
- 10/10/01 Submitted letter requesting a written confirmation on the acceptance of "Myfortic" as the proprietary trademark name for this compound.
- 10/15/01 TELECON with FDA to discuss a meeting date for the pre-NDA meeting.
- 10/24/01 FAX from FDA in response to a biowaiver request (Serial No. 068)
- 10/25/01 Submitted Amendment No.1 to Study No. B301.
- 11/02/01 FDA LETTER scheduling a Type B meeting in response to Novartis' October 29, 2001, request.
- 11/13/01 Submitted Briefing Book in preparation for the pre-NDA meeting scheduled for December 14, 2001.
- 11/15/01 Submitted amendment supporting changes in both the drug substance and drug product.
- 11/26/01 Submitted new protocol, Study No. 0108 (Part A) entitled: "A randomized, open-label, two-phase, four-period, crossover study to compare the steady-state pharmacokinetics and absolute bioavailability of ERL080 in stable renal transplant recipients during concomitant Neoral treatment and during concomitant tacrolimus treatment".
- 12/04/01 FAX from FDA containing comments on the pre-NDA briefing book (Serial No. 072).
- 12/10/01 Submitted new investigator to Study No. 0107: J. Zaltzman, MD
- 12/10/01 Submitted Amendment No.1 to Post-Text supplement 1 (extension Protocol 1) to Protocol ERLB 301; Amendment No.1 to Post-Text supplement 1 (Extension Protocol 1) to Protocol ERLB 302
- 01/10/02 FAX from FDA containing comments on Study No. 0108, Serial No. 074.
- 01/10/02 Submitted correspondence containing the list of Novartis representatives that attended the pre-NDA meeting held on December 14, 2001, as well as the slides presented.

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- 02/05/02 Submitted new protocols: Study No. CERL080A2405-US01 entitled, "One year, multicenter, open-label, prospective, randomized study to compare the effect of two Neoral C-2h maintenance targets, beyond two months post-transplant, on renal function, in the context of an immunosuppressive regimen consisting of Myfortic, Simulect, and steroids". Study No. CERL080A2401 entitled, "A 12-month, single-blind, randomized, parallel group, multicenter study to investigate the efficacy and safety of ERL080A compared with MMF in de novo heart recipients".
- 02/22/02 FAX from FDA containing the minutes of the December 14, 2001, pre-NDA meeting with the Division to discuss the preclinical, clinical, and biopharmaceutical aspects of the proposed NDA.
- 02/22/02 Request for a teleconference with the Division to obtain clarity on the Division's post meeting discussion regarding the December 14, 2001, pre NDA meeting.
- 02/25/02 Submitted amendment providing documentation supporting changes in the drug product, placebo and comparator.
- 02/25/02 Submitted briefing material for March 5, 2002 teleconference to discuss concerns on the higher exposure of mycophenolic acid indicated in the pharmacokinetic portion of Study B301.
- 03/04/02 Submitted Novartis' minutes from the December 14, 2001 pre-NDA meeting.
- 03/08/02 In response to an FDA request at the December 14, 2001 pre-NDA meeting, this submission contains preclinical reports for review by the Executive Carcinogenicity Assessment Committee (CAC).
- 03/15/02 FDA minutes of the March 15, 2002 Type C meeting to discuss the results of the Berlin pharmacokinetic study and the proposed design for Study 2302.
- 03/22/02 FAX to FDA containing a list of attendees for the March 15, 2002, teleconference.
- 03/22/02 Submitted new investigator for Study No. 2405: H. Meier-Friesche, MD
- 03/25/02 FAX from FDA containing comments on Studies No. 2405 and 2401 (Serial No. 078)
- 04/06/02 Submitted a copy of Novartis' minutes of the March 15, 2002, teleconference.
- 04/10/02 FDA LETTER asking Novartis to determine if the new protocol submitted February 5, 2002, Serial No. 078, meets the requirements for listing in the Clinical Trials Data Bank.
- 04/30/02 Submitted correspondence containing revisions to the FDA minutes of the March 15, 2002 teleconference.

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04/30/02 Submitted new investigator to Study No. A2401: H. J. Eisen, MD

05/07/02 Submitted a point by point response to FDA comments received March 25, 2002.

05/22/02 Submitted extension Protocol 1 to Protocol No. US01 entitled, "A prospective, open-label, multicenter, follow-up study on the efficacy and safety of Myfortic (ERL080A) in kidney transplant recipients".

05/23/02 In reference to the teleconference held on March 15, 2002, submitted a final version of Protocol No. ERL080 2302 (Pharmacokinetic Study) and asks for agreement on the modifications made.

05/23/02 Submitted correspondence requesting an update on the review of the tradename, Myfortic, and backup names.

05/23/02 Submitted new investigator to Study No. A2401: J. Kobashigawa, MD; to Study No. US01: B. Bresnahan, MD, H. Meier-Kriesche, MD

05/24/02 Submitted new investigators to Study No. US01: Drs. S. C. Jensik, G. Klintmalm, P. C. Kuo

06/06/02 Submitted new investigators to Study No. A2401: Drs. G. G. Renlund, G. M. Mullen

06/18/02 Submitted new investigator to Study No. A2401 and Study No. 2401 E1: K. Aaronson, MD

06/21/02 TELECON with FDA regarding the status of the CAR report review and a request for the CAR reports electronically

06/25/02 FAX from FDA containing comments on Study No. 2302 (Serial No. 088)

07/08/02 Submitted correspondence responding to the Division's comments of June 25, 2002, to Study No. 2302 (Serial No. 088)

07/15/02 FAX from FDA regarding Novartis' proposed tradename, Myfortic (Serial No. 069)

07/25/02 FAX from FDA containing comments on Serial No. 091 and 098

08/05/02 TELECON with FDA regarding the UCLA GCP audit findings and Novartis' intent to inform DSI

08/06/02 FAX from FDA containing a list of attendees for the July 29, 2002 telecon

08/08/02 In reference to a telephone conversation on August 5, 2002, regarding a GCP audit, submitted correspondence providing written notification to the file with a copy of the letter submitted on August 6, 2002, to the Division of Scientific Investigations.

IND PERIOD

- 08/13/02 Submitted new protocol and Amendments No.1 and 2 to Study No. CERL080A2302 (Part A) entitled, "An open label, two-treatment, two-period crossover study to compare mycophenolic acid exposure after 28-day treatment of 720 mg bid ERL080 (Myfortic) and after 28-day treatment of 1000 mg bid mycophenolate mofetil (CellCept) in stable renal transplant recipients". Investigator: H. T. Silva
- 08/14/02 In response to an FDA request regarding the carcinogenicity final study reports (Serial No. 084), submitted electronic datasets
- 08/29/02 Submitted new protocol: Study No. CERL080A2301 entitled, "A Randomized, Open-Label, Two-Period, Crossover Study to Compare the Steady-State Pharmacokinetics of ERL080 in Stable Renal Transplant Recipients during Concomitant Neoral Treatment and during Concomitant Prograf Treatment". Investigator: B. Kaplan, MD
- 09/27/02 Submitted Amendment No.3 to Study No. CERL080A2302.
- 10/01/02 FAX from FDA containing comments on protocol A2301, Serial No. 102.
- 10/02/02 Submitted [France] Dr N Lefrancois; Renal artery thrombosis, anuria, blood creatine increased, nephrectomy
- 10/10/02 FDA LETTER asking Novartis to determine if the new protocol submitted August 13, 2002, Serial No. 100, meets the requirements for listing in the Clinical Trials Data Bank
- 11/12/02 Submitted Amendment No.4 to Study No. CERL080 A2302 "
- 11/13/02 Submitted new protocol: Study No. CERL080A2404 entitled, "A twelve-month, randomized, multicenter, open-label study to investigate the clinical outcomes of two immunosuppressive regimens of Myfortic with short-term steroid use or free of steroids compared with a regimen of Myfortic with standard steroids in de novo kidney recipients receiving Simulect and Neoral - FREEDOM Study."
- 11/19/02 Submitted new investigators to Study No. US01: Drs. S. Inokuchi, P. Baliga
- 01/03/03 FAX from FDA containing comments on Study No. CERL080A2404, Serial No. 107.
- 02/03/03 Submitted new investigators to Study No. US01: Drs. D. J. Cohen, J. J. Curtis; Study No. A2401: Dr. M. J. Zucker
- 02/07/03 TELECON with FDA regarding the review status of the carcinogenicity studies submitted March 2002.
- 02/14/03 Response to comments received January 3, 2003, regarding protocol A2404 (serial No. 107)

IND PERIOD

- 03/17/03 In follow-up to the pre-NDA meeting held December 14, 2001, submitted the results of Study 2302 and the scheduled submission of the NDA.
- 03/21/03 Submitted Amendment No.1 to Study No. 2404
- 04/09/03 Submitted Annual Report covering the period October 7, 2001 through October 6, 2002. Includes individual study information, summary of safety information, list of death and dropouts, clinical information, preclinical study, CMC changes and foreign marketing developments.
- 04/11/03 Submitted new investigators to study No. US01; Drs. E.Benedetti, W. M. Bennett, J. Leone, F. Vincenti.
- 05/12/03 Submitted new investigators to Study No. A2401: Dr. B. Pisani; Study No. A2404: Drs. K.A. Bodziak, D. R. Holt, M. Pescovitz.
- 07/09/03 Submitted [France] Dr. Chantal Bouloux; Agranulocytosis, neutropenia, leucopenia NOS, pyrexia, vomiting NOS, diarrhoea NOS.
- 08/05/03 TELECON with FDA to discuss the potential for an FDA advisory committee and whether clinical sites are to be audited.
- 08/08/03 Submitted [France] Dr. Delphine Morel; Neutropenia, bone marrow toxicity, granulocytopenia.
- 08/21/03 Submitted new investigator to Study No. A2404: Drs. R. M. Ferguson, H. Sollinger.
- 09/11/03 Submitted [France] Dr. Delphine Morel; Neutropenia, bone marrow toxicity, granulocytopenia; Follow-up#1
- 09/19/03 Submitted [Belguim] Dr. Jean Louis Bosmans; Neutropenia, leukopenia NOS, Iliac artery, stenosis, hypertension NOS, stent insertion NOS; Follow-up#1
- 09/23/03 Submitted [France] Dr. Lionel Rostaing; Neutropenia.
- 11/13/03 Submitted Annual Report covering the period October 7, 2002 through October 6, 2003. Includes clinical study information, preclinical study information and a Foreign marketing developments.
- 12/02/03 Submitted [Australia] Dr. Paul Trevillian; Neutropenia.
- 12/31/03 Submitted [France] Dr. Lionel Rostaing; Neutropenia.
- 01/02/04 Submitted [Canada] Dr. A. Shoker; Neutropenia, renal disorder, leukopenia, blood creatinine increased.

IND PERIOD

- 01/06/04 Submitted [Canada] Dr. A. Shoker. Neutropenia, ureteric stenosis, leucopenia, perinephric collection, hydronephrosis, blood creatinine increased; Follow-up#1
- 01/12/04 Submitted [Australia] Dr. Paul Trevillian. Neutropenia: Follow-up#1
- 02/13/04 Submitted Investigator's Brochure, Edition 6, dated January 16,2004.

NDA PERIOD

- 04/30/03 Submitted original NDA for Myfortic delayed release tablets is indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal transplants, administered in cyclosporine, USP (Modified) and corticosteroids. (178 Vols + I E Vol)
- 05/14/03 FDA LETTER acknowledging receipt of original NDA dated April 30, 2003.
- 06/12/03 FAX to FDA regarding site activities and inspection readiness for Cardinal Health, Philadelphia, PA.
- 06/16/03 Response to FDA for information to clarify an issue raised concerning a reference made to Lilly's product, Melbex.
- 06/16/03 Response to request for a complete desk copy of the CMC section of the NDA.
- 06/19/03 Response to FDA request for a copy of the CRFs on compact disks (originally submitted on DL T tape).
- 06/20/03 Response to FDA request for information regarding the list of sites provided in the NDA.
- 07/11/03 FDA LETTER stating that the Division did not identify any potential filing review issues.
- 08/28/03 Submission of the 120-day Safety Update. (14 vols)
- 09/24/03 TELECON with FDA regarding clarification on the Kundl manufacturing site address and its CFN #.
- 10/08/03 Submitted amendment containing a replacement page that is being provided for each location indicating the correct CFN 9610016 (site number for Biochemie GmbH, Kundl).
- 10/09/03 TELECON from FDA regarding the outcome the first review assessment meeting that was held October 8, 2003.
- 10/17/03 TELECON with FDA to discuss comments received from the chemistry reviewer on October 9, 2003, regarding the container/closure components.
- 10/23/03 TELECON with FDA to discuss comments received from the chemistry reviewer on October 9, 2003, regarding the drug substance residual solvents specifications.
- 11/13/03 E-mail from FDA containing a request for CRF information from the Medical Officer.
- 11/19/03 TELECON with FDA to discuss the status of the Division's internal review assessment meeting held on November 18th.

NDA PERIOD

11/21/03 E-mail from FDA regarding validation of adverse reaction results in Study 8301 and efficacy analysis for Study 8302.

11/26/03 Response to FDA CMC comments dated October 9, 2003.

12/01/03 TELECON with FDA to discuss the status of the NDA and the mycophenolic acid DMF 15824 deficiency response letter.

12/02/03 Minutes from the Executive CAC Meeting held December 12, 2003.

12/02/03 Response to FDA for information on Studies 8301 and 8302 received in an e-mail dated November 21, 2003.

12/02/03 E-mails to/from FDA regarding list of participants at the December 1, 2003, teleconference.

12/04/03 TELECON with FDA regarding the status of the NDA review.

12/04/03 Response to FDA for copies of additional scanned CRFs from Studies 8301 and 8302.

12/04/03 E-mails to/from FDA regarding CRFs and progress of the NDA review.

12/08/03 Submitted revised patent information.

12/11/03 In reference to the partial response to FDA CMC comments dated November 26, 2003, submitted correspondence containing the remaining requested documentation.

12/11/03 FAX from FDA stating the proposed proprietary name Myfortic is acceptable

12/11/03 E-mails to/from FDA regarding receipt of a response by the CMC reviewer.

12/17/03 Notification that DMF 15824 (mycophenolic acid) was updated in complete response to the list of deficiencies FDA provided to the DMF holder on September 26, 2003.

12/19/03 FAX from FDA containing clinical pharmacology requests for information

01/09/04 Submitted response to an FDA request for pharmacokinetic information received December 19, 2003.

01/13/04 Submitted correspondence responding to a pharmacology/toxicology information request

02/05/04 E-mails to/from FDA regarding revised labeling.

NDA PERIOD

- 02/06/04 Minutes of a teleconference to discuss myfortic pediatric dosing and FDA's revised myfortic USPI.
- 02/06/04 E-mail to FDA containing a list of Novartis attendees during the February 6, 2004 teleconference.
- 02/13/04 Submitted alternative proposals to the package insert text recommended by the Division and indicates that Novartis will submit final labeling utilizing the "mycophenolic acid" established name as directed by the Division
- 02/13/04 E-mail from FDA regarding established name references.
- 02/17/04 TELECON with FDA regarding the rescheduled teleconference to discuss the package insert.
- 02/18/04 Responded to an FDA request for patient identifications on patients lost to follow-up after having a biopsy-proven acute rejection but prior to a graft loss/death by 12 months in Studies 301 and 302.
- 02/19/04 Response to an FDA request to identify parts of the application and label that rely on information Novartis does not own or which does not have a right of reference.
- 02/20/04 TELECON with FDA to clarify the inclusion of the new toxicology statement in the package insert.
- 02/23/04 E-mail containing FDA's revised package insert and information regarding the teleconference scheduled to discuss the post-approval commitment to conduct peri- and post-natal rat study.
- 02/23/04 Telecon with FDA regarding the status of the NDA review.
- 02/23/04 FAX from FDA containing chemistry recommendations for cGMP compliance.
- 02/23/04 Submitted correspondence stating the Novartis has accepted the Division's mouse carcinogenicity language into the package insert
- 02/25/04 Minutes of a teleconference to discuss a post-approval commitment to conduct a peri and post-natal study in rats.
- 02/25/04 Responded to a request for an updated list of countries where Myfortic is approved and the Myfortic Summary of Product Characteristics approved by the Concerned Member States of the European Union via Mutual Recognition Procedure on February 9, 2004.
- 02/25/04 Submitted correspondence containing the plans to conduct a peri- and post-natal study in rats as a post-approval commitment. Novartis also acknowledges receipt of FDA's recommendation regarding Microbial Testing.

NDA PERIOD

- 02/25/04 Submitted proposed final labeling.
- 02/27/04 Submitted proposed package insert and container labels for 180 mg and 360 mg tablets.
- 02/27/04 FDA LETTER approving this new drug application.